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**APPLICATION NUMBER: 60/611,853**

**FILING DATE: *September 21, 2004***

**RELATED PCT APPLICATION NUMBER: *PCT/US05/07264***



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092104

15992 U.S. PTO

PTO/SB/16 (04-04)

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
A MULTI-GENERATIONAL MULTI-CHEMISTRY APPROACH TO STRUCTURED POLYMERS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
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ENCLOSED APPLICATION PARTS (check all that apply) <u>630-690-5132</u>					
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<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.					
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Respectfully submitted,

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[Page 1 of 2]

Date

REGISTRATION NO.

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Docket Number:

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[Page 2 of 2]

Number 2 of 2

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## **TITLE OF INVENTION**

**A Multi-Generational Multi-Chemistry Approach to Synthesis of Structured Polymers**

## **INVENTOR**

**Krzysztof Matyjaszewski and James Spanswick**

## **CROSS REFERENCES TO RELATED APPLICATIONS**

**None**

## **STATEMENT REGARDING FEDERALY SPONSERED RESEARCH**

**None**

## **FIELD OF INVENTION**

**The invention is directed towards the synthesis of multi-generational structured polymers including dendrimers in a one pot reaction. This task can be accomplished by a multi-chemistry approach to dendrimer formation that is conducted by selecting the functional**

groups on each generation forming monomer to undergo reactions essentially only with the functional groups on the adjacent generation. The resulting dendritic molecules can be tailored to be more responsive to their target environment than present dendritic molecules since they are multilayered structures wherein each connecting layer can comprise different linking groups. When one of more of the generation forming monomers comprise oligo/polymeric materials then dendrimers with linear spacers are formed. Structured branched copolymers can be formed when one or more of each generation forming monomer comprises only two different functional groups. When each generation forming monomer comprises only two different functional groups then linear multi block copolymers with designed sequence of blocks are formed.

## BACKGROUND TO INVENTION

The invention will first be discussed by examining the preparation of dendrimers. Dendrimers are typically synthesized by a repetitive reaction using a branched  $A-B_x$  reagent via either a divergent or a convergent approach. (The bond in the representative generation forming monomer,  $A-B$ , can comprise a small molecule or an oligo/polymeric species) (Figure 1 and Grayson, S. M.; Frechet, J. M. J. *Chemical Reviews* **2001**, *101*, 3819-3867.) Repetition of the coupling and activation steps leads to an exponential increase in the number of reactions at the periphery; therefore, a large excess of reagents is required to drive both coupling and activation reactions to completion. However this procedure preserves the highly branched and highly regular dendrimer structures. A highly efficient protection/deprotection chemistry is required to prevent the possibility of

continuous formation of new dendrons (convergent) or new dendrimers (divergent) at each step. Unless control is exerted over each step of the multi-step process, spontaneous (or catalyzed) reaction of  $AB_x$  monomers via either condensation or addition reactions results in highly branched (hyperbranched) polydisperse macromolecules can occur and the value of the polydispersity index approaches that of the degree of polymerization (DP). High DP reached at high conversion leads to infinite polydispersity, like in a system approaching gel-point. Despite the difficulties encountered in their synthesis dendrimers are finding utility in bio-applications, electronics, and exchange media but the long involved multi-sequence preparation procedure keeps the costs high. A simpler process for preparation of structured polymeric materials is needed. Further a process for preparation of multi-responsive dendrimers is desired.

## DESCRIPTION OF DRAWINGS

Figure 1. Schematic summarizing present approaches to dendrimer synthesis.

Figure 2. Schematic of four monomer units and core monomer exemplifying the single pot construction of a four generation functional dendritic molecule.

## DETAILED DESCRIPTION OF THE INVENTION

We herein propose a new synthetic approach for the preparation of regular dendrimers in high yield without the protection/deprotection/separation procedures required in prior art synthetic processes and further teach how this approach to structured materials can be

extended to synthesis of branched copolymers and linear copolymers with designed sequence distribution of polymer segments. In contrast to known conventional methods for the synthesis of dendrimers which rely on a single chemistry for bond formation (except last optional functionalization step), Figure 1, the disclosed approach employs multiple linking chemistries that do not interfere one with another, Figure 2. The later figure is a graphical representation of the multi-chemistry approach. Each fragment of the final intergenerational linking group is shown in the same color and link shape is chosen to further illustrate the exclusive nature of the multi-chemistry for each generation of monomer linking. The illustration of the linking chemistry is selected so that the each generation of the dendrimer must assembly by colors and by shape. (The colors and shape representing specific functional groups that will selectively and exclusively react with each other.) So it would result in the layered (rainbow) of linked objects, if stoichiometry is preserved. In the ideal case, all reagents could be combined together, in stoichiometric amounts, and a multi-generational dendrimer would be formed in a simple one pot process, a one pot process with sequential addition of monomers, or in a continuous multi-flask process.

In the one pot process the dendrimers self-assemble by a mixture of convergent and divergent steps, depending on the relative rates of each particular generation forming step. The rate of each generation forming reaction will obviously not only depend on the rate constants for each generation forming reaction (and concentration of catalysts for catalyzed reactions) but also on the concentration of functional groups. Thus, the more reactive species could be placed closer to the core if one wishes to construct the



dendrimer in a divergent procedure. The requirements are that each generation forming reaction proceeds with high selectivity and in high yield and further that the functional groups in each generation do not interfere in the earlier generation chemical bond formation reactions. As such the approach can be considered to be a multi-chemistry approach to dendrimers, or an approach to multi-orthogonal molecules since the chemistry can be selected to form three dimensional molecules, in which the resulting dendritic molecules will be more responsive to their environment than present dendritic molecules since they are multilayered structures wherein each connecting layer can comprise different linking groups that can be selected to be responsive in different manners to the encountered environments.

It is also possible to mix reagents stepwise to avoid some potential interference between certain reactions or utilize a continuous multi-flask process for the synthesis. In the continuous multi-flask process of the growing dendrimers, or dendrons, could be transferred from reaction flask to reaction flask with the removal of catalytic amounts of reagents, or transformation of catalyst species occurring between reaction flasks. This would allow sequential high yield reactions to proceed in the absence of trace contaminants or catalysts from one step that could affect the yield of the next step.

The result of this *Multi-Chemistry Dendrimer* (MCD) approach to dendrimer formation, in contrast to *Single-Chemistry Dendrimer* (SCD), previously practiced is that the materials will have a layered structure and each generation will be characterized by a different linking unit resulting from each specific generation linking chemistry. The units

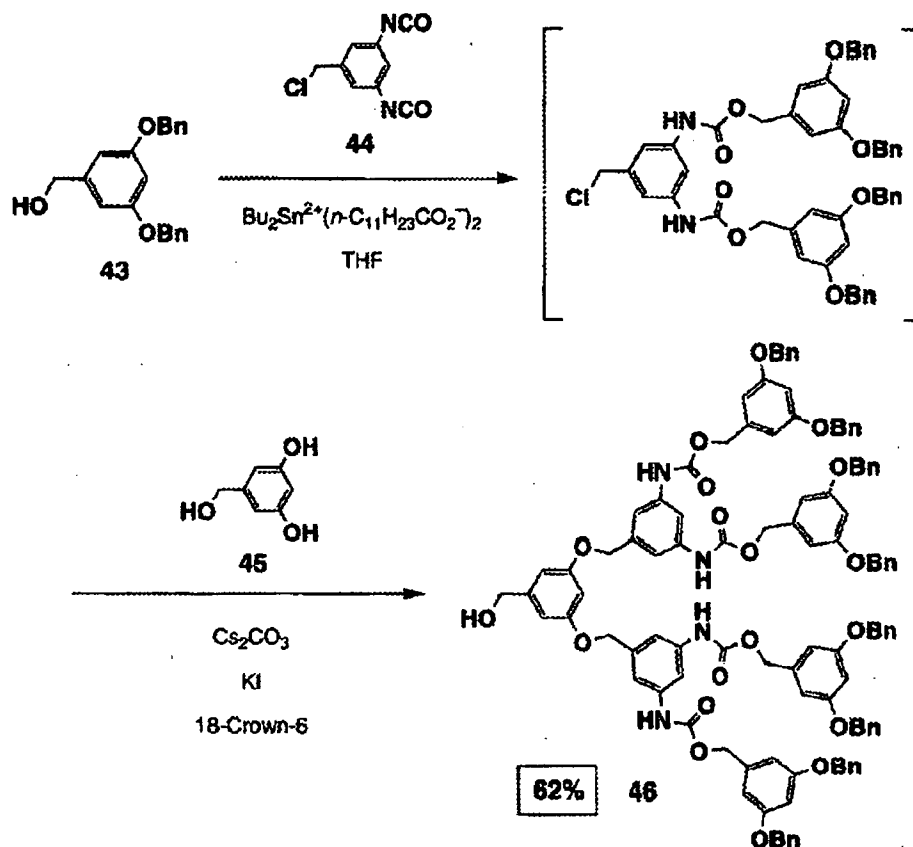
connecting each generation can have different, and optionally even oligo/polymeric, structures. This can help in self-assembly of units at each generation. A further consequence of this approach to dendrimer synthesis is that within the molecule there are layers of different functionality that can impact the intramolecular properties of the material and hence the utility of the molecule for selective adsorption or desorption of small molecules. Further the organized intramolecular structure can be utilized to provide for self assembly of the formed dendrimers into macro-structures.

As noted above the same concept could be used to prepare multi-segmented block copolymers (linear or not) such as ABC or ABCD by selecting the end functional groups on each precursor copolymer segment to allow only coupling or chain extension with the desired next polymer segment.

If the functional groups on the termini of well defined segmented copolymers are selected in the same manner as for MCD then dendrimers with spacers (from linear chains) will be formed. Such dendrimers can be considered to have similar topology and utility to the compact dendrimers of the present art but the free volume within the dendritic structure can be modified to allow significantly more bio-functional materials to be incorporated within the molecule thereby increasing their utility as media for delivery of substances, organic or inorganic, in *in vivo* applications.

There has been one attempt to conduct a multiple chemistry dendrimer synthesis. Frechet [J. Chem. Soc., Perkin Transactions 1, 1993, 913-918] attempted to conduct a "two-step"

sequential approach. In this approach, two different monomers are used (Scheme 1) to avoid the need for an activation step between growth steps. The two monomers have an  $AB_2$  and  $CD_2$  structure, where A and D react to form a bond under conditions where B and C are stable, and B and C react to form a bond under conditions where the first formed A-D link is stable. Convergent or divergent growth is theoretically possible using this method. In the particular system developed by Frechet, the two reactions used are the Williamson ether synthesis and the formation of a urethane from an isocyanate and an alcohol. The chemistry is shown in detail in Scheme 1, using the monomers 3,5-diisocyanatobenzyl chloride and 3,5-dihydroxybenzyl alcohol. The surface moiety, (3,5-dihydroxybenzyl alcohol (43)) is first reacted with monomer 3,5-diisocyanatobenzyl chloride (44) then, monomer (45) is added to the reaction mixture. This one-pot reaction gives the second-generation wedge (46) directly from surface and monomer units in 62% yield.



Scheme 1. A single pot “two step” approach to dendrimer synthesis (from [J. Chem. Soc., Perkin Transactions 1, 1993, 913-918]; note the limited yield of 62%).

Although this approach enabled a one-pot, two-step synthesis of the third generation poly(ether carbamate) dendron the low yield and resulting difficulties in purification prohibited further growth. These difficulties were such that the technique was not pursued further particularly as the present dendrimer-making requirements, defined by Frechet, call for very “clean” high yield reactions at each and every step in the reaction sequence.

Figure 2 shows a simplified schematic of four monomer units for single pot construction of a four generation functional dendritic molecule exemplifying the present disclosure. The figure also includes a simplified schematic of the intergeneration chemistry showing only one of A', B', C' and D' groups reacting with the next generation that is provided for clarification. This simplified schematic also provides a visualization of the approach that can be utilized to form a linear multi-segmented copolymer, (i.e. if one assumes the second function A', B', C' and D' groups are not present). In figure 2 the core molecule is shown with only one core functional group "X". The core molecule could be a multifunctional molecule such as a tetramine, resulting in the direct formation of a multi-branch dendrimer. Further, as noted above, if one or more of the species represented by a single symbol in each generation forming molecule is an oligo/polymer species then a highly tailored branched polymer structure could be formed.

The key issue is the selection of the chemistry for each generation forming linking reaction which should not interfere one with another. *I.e.* A would only react with A' and B would only react with B' etc..... The next generation would comprise different functional groups that would react under different conditions. As noted above the only requirement is that the functional groups in each generation do not interfere in the earlier generation chemical bond formation reactions. For example one generation could be formed by a hydrosilation reaction, (A = H-Si and A' = an olefin) another generation could be formed by an ATRA between -SO<sub>2</sub>Cl (B) and an olefin (B' = R<sup>1</sup>,R<sup>2</sup>-C=C-R<sup>3</sup>,R<sup>4</sup>); or through use of a 2+3 cycloaddition reaction between an acetylene and an alkyl azide via "click chemistry". Indeed, all chemistries that meet the requirements of "click

chemistry”; most frequently exemplified by this Huisgen 1,3-dipolar cycloaddition of acetylene and an alkyl azide forming a triazole ring; initially defined by Sharpless [Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angewandte Chemie, International Edition* 2001, 40, 2004-2021] would operate as linking chemistries in MCD. Indeed the requirements of “click chemistry” are almost the requirements for MCD. Sharpless defined “click chemistry” as a reaction that must be modular, wide in scope, give very high yields and generate only inoffensive by products. Sharpless further noted it is important to recognize that “click chemistry” reactions achieve their required characteristics by having a high thermodynamic driving force, usually greater than 20 kcalmol<sup>-1</sup>. Such processes proceed rapidly to completion and also tend to be highly selective for a single product: these reactions can be thought of as being “spring-loaded” for a single trajectory. Therefore all individual “click chemistries” discussed by Sharpless are candidates for one of the generation forming linking chemistries along with those chemistries exemplified below as high yield linking chemistries.

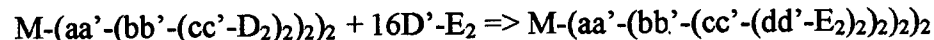
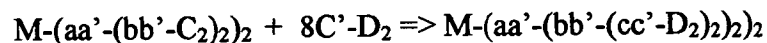
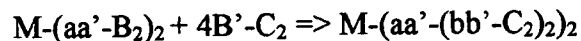
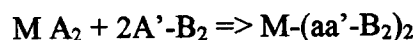
The problems that are likely to be encountered in MCD arise from the difficulty in finding a set of reactions which conform to the above criteria as well as the usual dendrimer-making requirements of very “clean” chemistry that proceeds in high yields, at every step in the reaction sequence. Therefore the generation forming reactions must be selected with care; since if one decides to employ a Michael reaction of electron poor alkenes with primary or secondary amines, the latter will compete with alcohols selected to participate in urethane formation. Similar interference will be encountered for a reaction between amines and carboxylic acids and Michael addition. Also, the very

selective atom transfer radical addition of sulfonyl halides to alkenes should be used in the absence of amines or alcohols, etc. Nevertheless, these reactions could be still used in a one-pot but two step approach, when the monomer utilizing amines as one functional group in the generation forming linking chemistry could be added only after the alcohol is totally consumed or sulfonyl halide reacted with alkenes.

The new concept relies on a mixture of convergent and divergent approaches and will essentially follow the concept of self assembly. What is needed is a simple combination of several different chemistries which should occur in high yield and high selectivity and should not interfere one with another. A stoichiometric mixture of compounds should be used. In this MCD approach to dendrimer formation one should have reaction exclusively between A and A', B and B', C and C', etc., and the presence of the reagents and catalysts needed for the reaction between B and B' as well C and C' should not affect the high selectivity of the A-A' reaction. Where there is a potential for interference then the reagents should be added sequentially, or the reactants can be transferred to a second flask, with an optional minimal purification step to remove either the contaminant formed or catalyst used in the earlier step conducted during the transfer process.

#### DISCUSSION OF PROCESS STEP(S).

In the above discussion the different functionality on the monomers that form each layer are represented by letters based on a binary system, which of course can be converted to multi-functional system to better represent dendrimer forming molecules:



First one should prepare reagents of the structures  $X-A_m$ ,  $A'-B_n$ ,  $B'-C_o$ ,  $C'-D_p$ , etc. The reagents should be present in the reaction at appropriate relative molar ratios:  $X-A_m$ :  $A'-B_n$ :  $B'-C_o$ :  $C'-D_p$ :... = 1 : m : m x n : m x n x o : ... If the chemistry for each generation forming step is selected with care then the system should assemble to  $X-(((A-A')_m-B-B')_{mn}-C-C')_{mno}-D_{mnop}$ ...etc.

Some examples of reactions which are known to proceed in high yield and in high selectivity and should not interfere one with another, or at least the products of these reactions should not interfere with the reagents used for another reaction, are:

- a) hydrosilation, reaction of H-Si and simple non-activated vinyl compounds
- b) urethane formation from alcohols and isocyanates
- c) 2+3 cycloaddition of alkyl azides and acetylenes
- d) Menshutkin reaction of tertiary amines with alkyl iodides
- e) Atom transfer radical addition
- f) Metathesis
- g) Staudinger reaction of phosphines with alkyl azides
- h) many of the procedures already used in dendrimer synthesis, especially in a convergent approach, which require high selectivity and rates, can also be



employed. There have been several review articles where such chemistry is discussed including:

- Hawker, C. J.; Wooley, K. L. *Advances in Dendritic Macromolecules* **1995**, *2*, 1-39;
- Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Progress in Polymer Science* **1998**, *23*, 1-56;
- Majoral, J.-P.; Caminade, A.-M. *Chemical Reviews (Washington, D. C.)* **1999**, *99*, 845-880;
- Grayson, S. M.; Frechet, J. M. J. *Chemical Reviews (Washington, D. C.)* **2001**, *101*, 3819-3867.

These reactions could occur optionally simultaneously (i.e. with similar rates) or not - or could be used sequentially in one pot – or sequentially in a series of pots. Spacers can be introduced to facilitate the reaction by self assembly and reduce steric effects and perhaps also make layered structures more likely. The spacers could optionally be oligo/polymeric species and can optionally comprise non-linking functional groups that could enhance the self-assembly of the spacers or be used later to enhance interaction with bio-active materials.

As noted above this system can also be extended to the preparation of regular linear multi-segmented block copolymers: where polymer segments with selected terminal functionality such as A'-P<sub>1</sub>-B, B'-P<sub>2</sub>-C, C'-P<sub>3</sub>-D and D'-P<sub>4</sub>-A can use the selective linking chemistry to make a linear A'(P<sub>1</sub>)B:B'(P<sub>2</sub>)C:C'(P<sub>3</sub>)D:D'(P<sub>4</sub>)<sub>n</sub> multiblock segmented

copolymer of controlled sequences of polymer segments, optionally with pre-selected chain end functionality.

Further if one or more of the first formed polymers are formed by controlled polymerization processes from multi-functional initiators then branched materials having generations of high molecular weight polymer between branching junctures emanating from a central core can be formed. The key issue is the selection of each layer forming chemistry or chain extension chemistry should not interfere one with another. The linking chemistry can be conducted in solution or in bulk. In the case of linking higher molecular weight polymer precursors the “one pot” could be an extruder, preferentially a twin screw extruder with devolatilization capabilities.

We have noted that the linking chemistries for MCD should be selected to minimize inter generational interference. Listed below are some examples of potential interference:

- a) Hydrosilation, H-Si and simple non-activated vinyl compounds – may compete with other alkenes, Pt catalyst may be deactivated by some functionalities;
- b) Urethane formation from alcohols and isocyanates – require absence of primary and secondary amines and absence of water;
- c) 2+3 cycloaddition of alkyl azides and acetylenes via “click chemistry” – may compete with phosphines used in a Staudinger reaction (f);
- d) Menshutkin reaction of tertiary amines with alkyl iodides– may compete with phosphines (f), polar solvents needed,

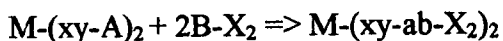
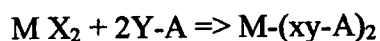
- e) ATRA, best  $\text{RSO}_2\text{Cl}$  with substituted styrene – may compete with alcohols and amines;
- f) Staudinger reaction or reaction of phosphines with azides – no acetylene and no alkyl iodides should be present;
- g) Michael addition of amines to alkenes with electron withdrawing groups may compete with amide formation (h)
- h) Condensation of amines or alcohols with acid – may compete with urethane formation or Michael addition

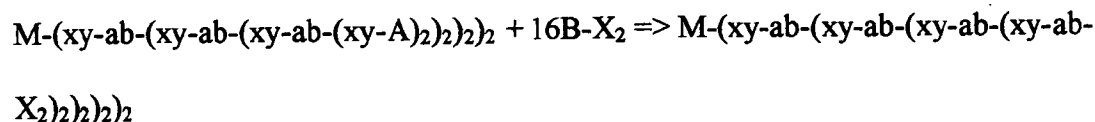
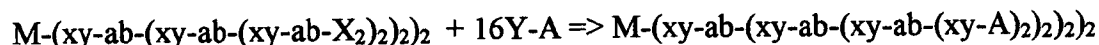
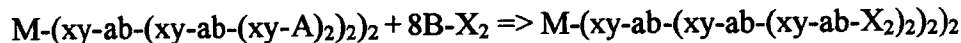
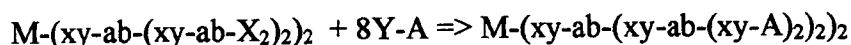
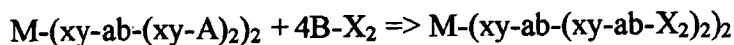
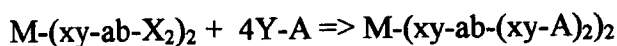
Other possible interfering chemistries are discussed by Stoddard and Frechet in their reviews.

This may indicate that sequential addition of monomers, or timed addition of monomers to linked multiple flasks, be considered for monomers comprising certain functionalities when that functionality could compete with the linking chemistry for a remote generation.

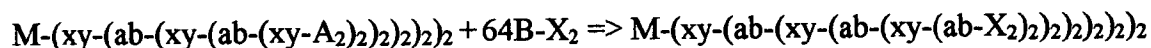
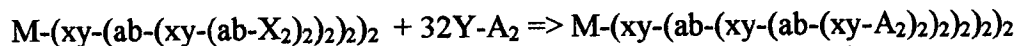
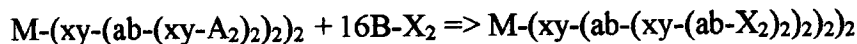
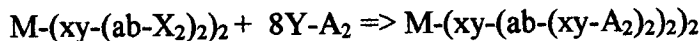
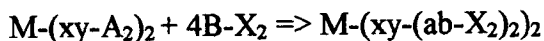
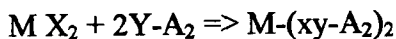
If the linking chemistries in  $\text{X-A}_m$ ,  $\text{A'-B}_n$ ,  $\text{B'-C}_o$ ,  $\text{C'-D}_p$  can be represented by  $\text{X+Y-}>\text{xy}$  and  $\text{A+B-}>\text{ab}$  and the functional groups are present at the termini of a polymer segment and that the extender segment is represented by an  $\text{YA}$  for a linear extender, or  $\text{YA}_2$  for a branched extender unit, then one or more possible generation sequences of linking chemistry would be:

$\text{YA}$  is extender:





YA<sub>2</sub> is branched unit:



As noted above suitable linking chemistries include high yield Michael addition reactions.

The following papers review Michael addition reactions. Due to their excellent yield, high selectivity, convenient operation and cost-effectiveness, eco-friendly solvent-free process conditions they have been extensively explored recently. Some new synthetic methods have been developed employing various highly efficient catalysts, which will definitely broaden the application of this reaction to the development of new materials, including MCD as disclosed herein.

- Betancort, J. M.; Barbas, C. F., 3rd *Organic Letters* **2001**, *3*, 3737-3740;
- Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Organic Letters* **2001**, *3*, 3753-3755.
- Highly diastereoselective Michael addition reactions of butane-2,3-diacetal desymmetrized glycolic acid. Preparation of  $\alpha$ -hydroxy- $\gamma$ -amino acid derivatives
- Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *Journal of the American Chemical Society* **2003**, *125*, 2582-2590. where the Michael addition of unmodified ketones using new asymmetric zinc catalysis are described. Yield (up to 99%),
- Bensa, D.; Constantieux, T.; Rodriguez, J. *Synthesis* **2004**, 923-927. P-BEMP: A new efficient and commercially available user-friendly and recyclable heterogeneous organocatalyst for the Michael addition of 1,3-dicarbonyl compounds.
- Lu, G.; Zhang, Q.; Xu, Y.-J. *Youji Huaxue* **2004**, *24*, 600-608.
- Chernaga, A. N.; Davies, S. G.; Lewis, C. N.; Todd, R. S. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1999**, 3603-3608. Stereoselective Michael addition of benzylamines.

Other Michael addition reactions include reactions of unmodified aldehydes with nitro olefins using (S)-2-(morpholinomethyl)pyrrolidine as a catalyst. The reactions proceed in good yield (up to 96%). Novel L-neopentylglycine derivatives as auxiliary for copper-catalyzed asymmetric Michael reactions and Michael additions of nitro compounds, thiols, and amines have also been described. All are potentially suitable for high yield linking chemistries suitable for MCD and the preparation of branched and linear segmented copolymers.

Another high yield dendrimer forming reaction is described in: Diez-Barra, E.; Garcia-Martinez, J. C.; Rodriguez-Lopez, J. *Tetrahedron Letters* **1999**, *40*, 8181-8184 where they describe a synthetic route to first generation 1,3,5-tris(phenylenevinylene) dendrimers based on the Horner-Wadsworth-Emmons reaction which provides for stereochemical control in preparation of dipolar and non-dipolar structures.

Yet another approach to high yield and high purity dendrimers is the stepwise convergent approach consisting of a combination of Williamson etherification and hydroboration/oxidation steps described in *Macromolecules* **2004**, *37*, 4227-4234.

Selective copper catalyzed "click chemistry" is described by:

- Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. "Efficiency and fidelity in a click-chemistry route to triazole dendrimers by the copper(I)-catalyzed ligation of azides and alkynes;" *Angewandte Chemie, International Edition* **2004**, *43*, 3928-3932.
- Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. "Huisgen 1,3-dipolar cycloadditions;" *Langmuir* **2004**, *20*, 1051-1053. The reactants, acetylenes and azides, are independently stable; they do not react with common organic reagents or with themselves.

- Demko, Z. P.; Sharpless, K. B. *Angewandte Chemie, International Edition* **2002**, *41*, 2110-2113-2116; a click chemistry approach to tetrazoles by Huisgen 1,3-dipolar cycloaddition: synthesis of 5-acyltetrazoles from azides and acyl cyanides
- Substituted 5-acyltetrazoles are prepared by a [2 + 3]-cycloaddition of readily available acyl cyanides with azides.

The copper(I)-catalyzed 1,2,3-triazole formation from azides and terminal acetylenes is a particularly powerful linking reaction, due to its high degree of dependability, complete specificity, and the bio-compatibility of the reactants. The triazole products are more than just passive linkers; they readily associate with biological targets, through hydrogen bonding and dipole interactions and as such may preferentially be placed near the shell of the final structure, or near an incorporated oligo/polymeric segment, to allow the greater free volume of the selected environment to accommodate the added agent.

Other high yield clean chemistry approaches have been described:

- Maraval, V.; Pyzowski, J.; Caminade, A.-M.; Majoral, J.-P. *Journal of Organic Chemistry* **2003**, *68*, 6043-6046. describe a green chemistry method for dendrimer synthesis using phosphazene hydrazine with only N<sub>2</sub> or H<sub>2</sub>O as byproducts
- Ihre, H.; Padilla de Jesus, O. L.; Frechet, J. M. J. *Journal of the American Chemical Society* **2001**, *123*, 5908-5917 describe fast and convenient divergent synthesis of aliphatic ester dendrimers by anhydride coupling.
- Carnahan, M. A.; Grinstaff, M. W. "Synthesis and Characterization of Poly(glycerol-succinic acid) Dendrimers;" *Macromolecules* **2001**, *34*, 7648-7655.

- Pasquato, L. *Speciality Chemicals Magazine* **2002**, 22, 21-22, 24 present a review on electrophilic oxidative additions to olefins that make up a family of chemical transformations that are particularly appealing to organic chemists, because they lead to regio- and stereocontrolled functionalization of the C-C double bond.

This latter class of reactions is an example of the carbon-heteroatom bond-forming process that meets the criteria of the “click chemistry” recently introduced by Sharpless. The reaction occurs in two steps: the first gives rise to the formation of the intermediate cyclic thiiranium ion, the second is the nucleophilic opening of the intermediate via an SN2 mechanism. Only a few electrophiles - sulfur, selenium and some halogens under appropriate conditions - add to alkenes via this general mechanism. Some recent examples of synthetic advances are presented in the papers with particular attention to new stereoselective processes and reactions in benign solvents, such as water.

Therefore we claim that by selecting high yield compatible linking chemistry from the non-limiting high yield chemistries described above it is possible to conduct the synthesis of multi-generational dendrimers by a multi-chemistry approach to dendrimer formation that is conducted by selecting the functional groups on each generation forming monomer to undergo reactions only with the functional groups on the adjacent convergent and divergent generations. Further the linking chemistry can be utilized to form branched copolymers and linear copolymers with designed distribution of polymer segment.

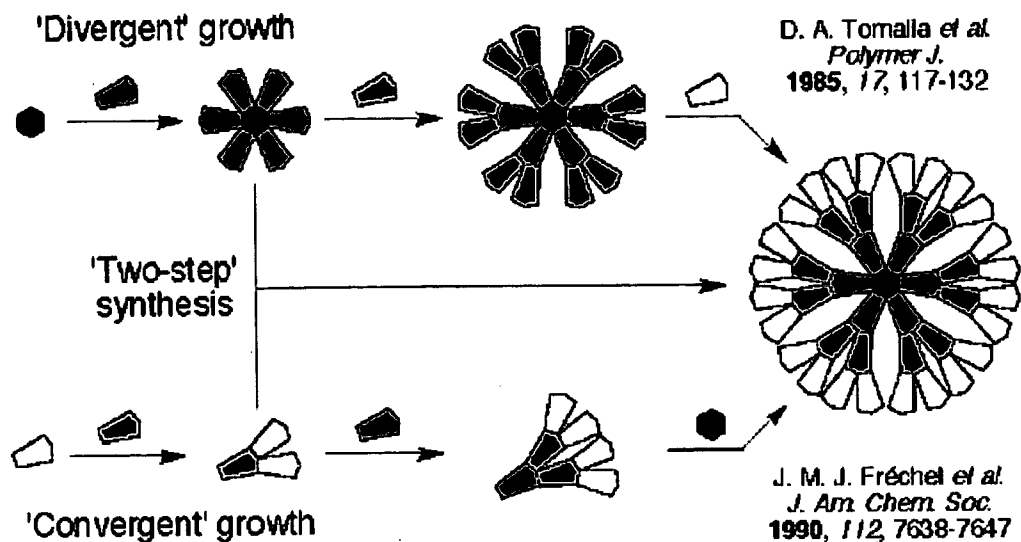


## CLAIMS:

1. A process for the synthesis of multi-generational dendrimers, branched copolymers or multi-segmented linear copolymers through a multi-chemistry approach to multiple bond formation wherein the functional groups for each linking chemistry are chosen to selectively undergo reactions only with the functional groups on the desired adjacent convergent and divergent generation in the dendrimer or the desired adjacent segment in the branched copolymer or the desired adjacent segment in a multi-segmented linear copolymer.
2. The process of claim 1, wherein the reactions are conducted in one pot.
3. The process of claim 1 wherein one or more reagents are added to the reaction at different times.
4. The process of claim 1 wherein the reaction medium is transferred from one reactor to another during the synthesis of the dendrimer, branched copolymer or multi-segmented linear copolymer.
5. The process of claim 4, wherein impurities or catalyst residues are removed during the transfer.

6. The process of claim 5, wherein one or more reagents are added to the sequence of reactions at different times or to different reactors.
  
7. The process of claim 1, wherein the dendrimer system assembles to  $X-(((A-A')_m-B-B')_{mn}-C-C')_{mno}-D_{mnop}\dots$  etc by selecting the different functionality on the monomers that form each layer or generation as represented by letters based on a binary system, wherein A reacts with A'; B reacts with B'; C reacts with C' and D reacts with D' etc which of course can be converted to multi-functional system to better represent dendrimer forming molecules as follows:  $X-A_m$ ,  $A'-B_n$ ,  $B'-C_o$ ,  $C'-D_p$ , etc. the reagents should be present in the reaction at appropriate relative molar ratios:  $X-A_m : A'-B_n : B'-C_o : C'-D_p : \dots = 1 : m : m \times n : m \times n \times o : \dots$  then the system can assemble to  $X-(((A-A')_m-B-B')_{mn}-C-C')_{mno}-D_{mnop}\dots$  etc.
  
8. The process of claim 7, wherein the bond present between the generation forming functional groups  $X-A_m$ ,  $A'-B_n$ ,  $B'-C_o$ ,  $C'-D_p$ , etc.. can represent a small compact molecule or an oligo/polymeric species.
  
9. The process of claim 1, wherein the selective functional chemistry is selected for the preparation of regular linear multi-segmented block copolymers with designed sequence distribution of polymer segments.

## The Construction of Dendrimers — 1



## The Construction of Dendrimers — 2

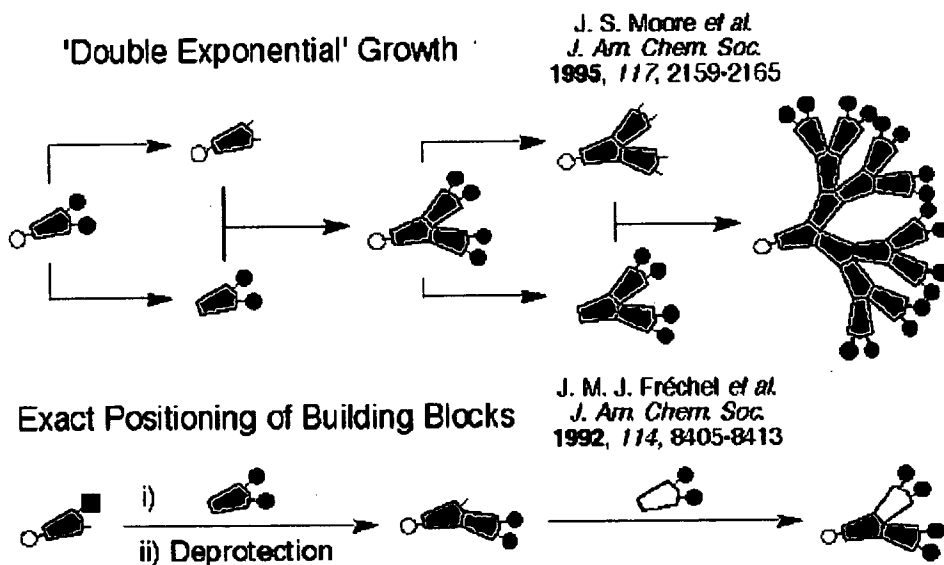


Figure 1. Construction of Dendrimers (from [*Progress in Polymer Science* 1998, 23, 1-56])

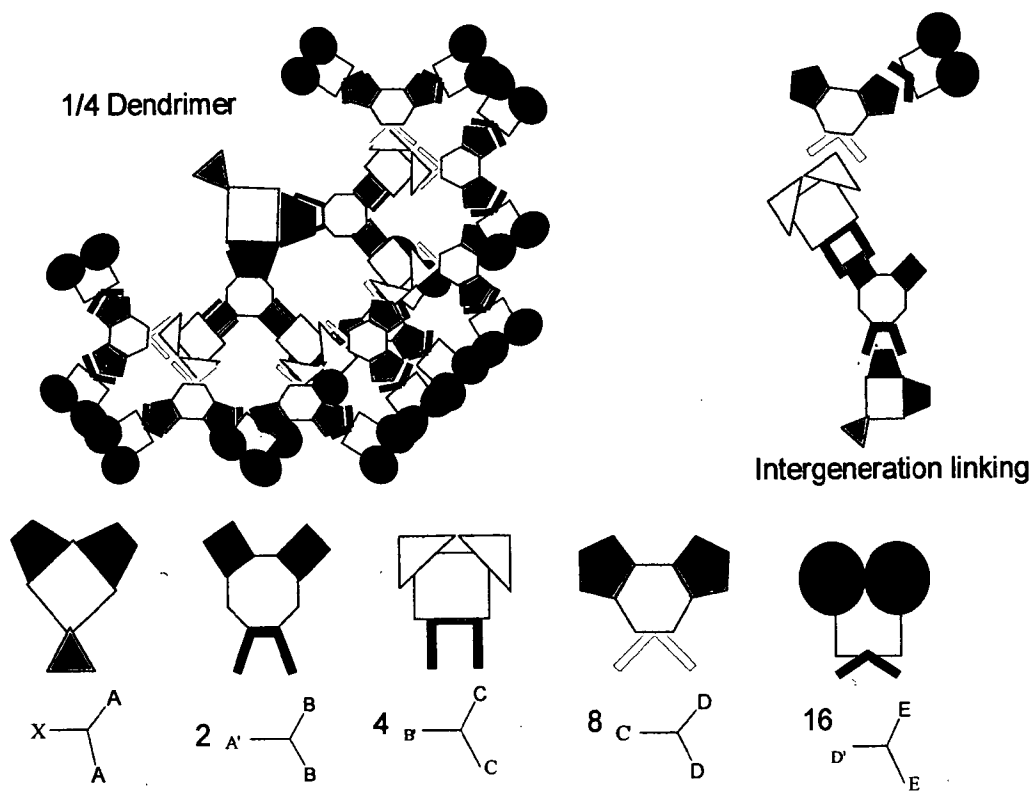


Figure 2. Schematic of four monomers that will react only with the next generation linking group in a multi-generational synthesis of dendrimers. The core molecule “X” could be a multifunctional molecule, such as a tetramine, resulting a multi-branch dendrimer.